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Tranexamic acid – A narrative review for the emergency medicine clinician

Kellie Wang, PharmD, BCCCP [a,*], Ruben Santiago, PharmD, BCCCP [b]

[a] Department of Pharmacy, Sarasota Memorial Health Care System, 1700 S Tamiami Trail, Sarasota, FL, USA
[b] Department of Pharmacy, Jackson Memorial Hospital, 1611 NW 12th Avenue, Miami, FL, USA

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ABSTRACT

Introduction: Over the last decade, tranexamic acid (TXA) has been incorporated into treatment algorithms for a multitude of emergent conditions and the evidence surrounding its role in emergency medicine continues to evolve.
Objective: The objective of this literature review is to provide an evidence-based approach to the utilization of TXA in the emergency department.
Discussion: The most robust trials suggest TXA may offer a modest improvement in mortality in patients at risk of significant bleeding from trauma, but is not beneficial in spontaneous intracranial hemorrhage or gastrointestinal bleeding. The role of TXA in other clinical scenarios is less clear and requires clinical judgment.
Conclusion: Tranexamic acid appears to be a reasonable adjunct for the emergency medicine clinician to consider in the management of many hemorrhagic conditions and angiotensin converting enzyme inhibitor-induced angioedema. Additional high-quality research in these areas is needed to further identity patients who may benefit most from TXA.

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1. Introduction

First synthesized in 1962, tranexamic acid (TXA) is still the subject of widespread clinical investigation. A growing body of literature has supported TXA in numerous bleeding conditions, and its application in other physiological processes is also being explored. Tranexamic acid is recommended in multiple guidelines and classified as an essential medicine by the World Health Organization (WHO) [1-6]. The purpose of this literature review is to provide an evidence-based approach to the utilization of TXA in the emergency department (ED).

2. Pharmacology, adverse effects, and administration considerations

Tranexamic acid is a synthetic lysine analog that inhibits plasminogen conversion to plasmin, which hinders fibrinolysis and clot degradation (Fig. 1) [7,8]. Tranexamic acid also prevents circulating plasmin from binding to fibrin, resulting in an inactive complex [7]. Additionally, TXA may modulate the inflammatory response to injury by limiting formation of plasmin, which possesses immunosuppressive and proinflammatory properties [9,10]. The fibrinolytic pathway also plays a role within the contact activation system, and inhibition of plasminogen activation by TXA hinders a crucial step in bradykinin formation (Fig. 1) [8,11].

Tranexamic acid is generally well-tolerated with mild adverse effects, such as gastrointestinal and visual disturbances (Table 1). Although less common, serious thromboembolic complications, including pulmonary embolism, deep venous thrombosis, and cerebral thrombosis are possible (Table 1) [7]. Tranexamic acid competitively inhibits glycine and gamma-aminobutyric acid receptors in the central nervous system, which may reduce the seizure threshold. Seizures associated with TXA are rare and the risk increases with higher dosing [12-14].

Abbreviations: ACE, angiotensin converting enzyme; ACEI-AE, angiotensin converting enzyme inhibitor induced angioedema; CRASH-2, Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage-2; CRASH-3, Clinical Randomisation of an Antifibrinolytic in Significant Head Injury-3; ED, emergency department; GCS, Glasgow Coma Scale; GIB, gastrointestinal bleeding; HALT-IT, Effects of a High-Dose 24-h Infusion of Tranexamic Acid on Death and Thromboembolic Events in Patients with Acute Gastrointestinal Bleeding; ICH, intracerebral hemorrhage; IV, intravenous; IM, intramuscular; IO, intraosseous; LOS, length of stay; MATTERs, Military Application of Tranexamic Acid in Trauma Emergency Resuscitation; NoPAC, The Use of Tranexamic Acid to Reduce the Need for Nasal Packing in Epistaxis; PATCH-Trauma, Pre-hospital Anti-fibrinolytics for Traumatic Coagulopathy and Haemorrhage; PTH, post-tonsillectomy hemorrhage; RCT, randomized controlled trial; SAH, subarachnoid hemorrhage; SBP, systolic blood pressure; STAAMP, Study of Tranexamic Acid During Air and Ground Medical Prehospital Transport; TBI, traumatic brain injury; TEG, thromboelastography; TICH-2, Tranexamic acid for Hyperacute Primary Intracerebral Haemorrhage; TXA, tranexamic acid; ULTRA, Ultra-Early Tranexamic Acid After Subarachnoid Haemorrhage; US, United States; UK, United Kingdom; WHO, World Health Organization; WOMAN, World Maternal Antifibrinolytic; VTE, venous thromboembolism.

* Corresponding author.
E-mail address: kelliemwang@gmail.com (K. Wang).

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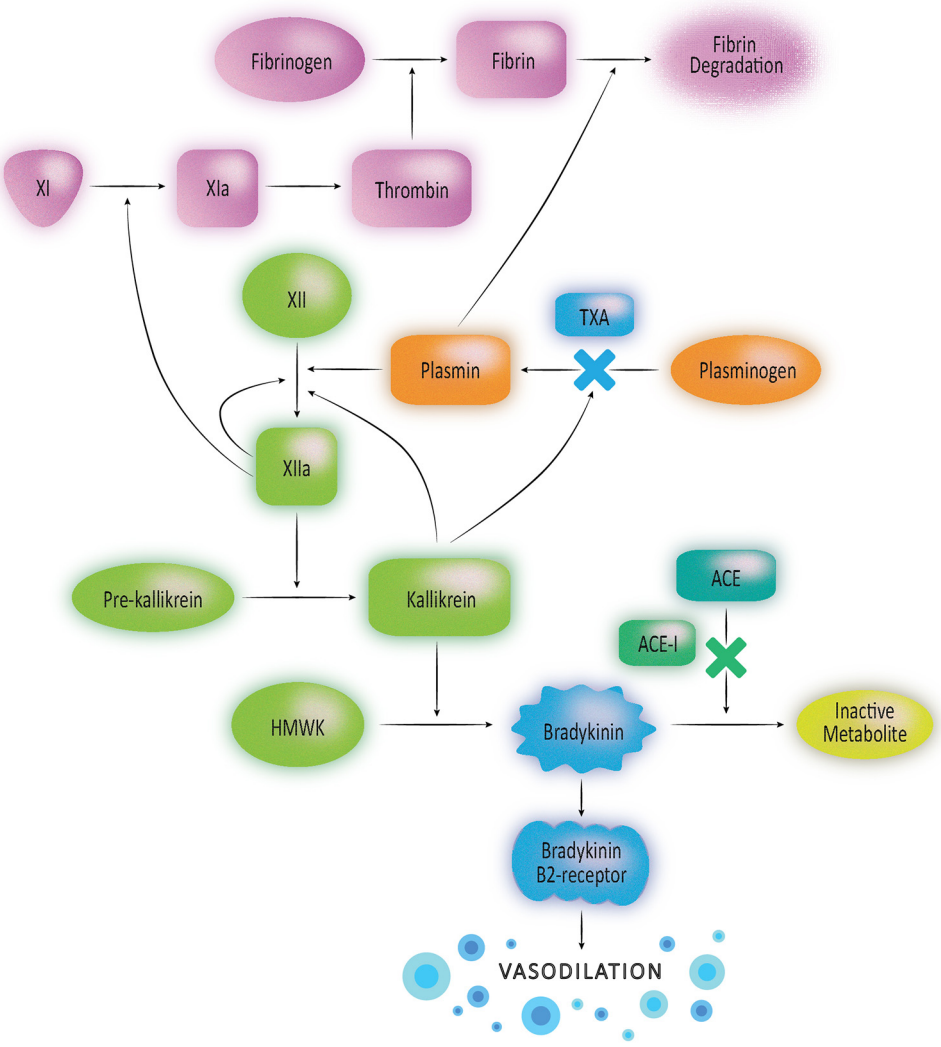

Fig. 1. Pharmacology of tranexamic acid in the fibrinolytic and bradykinin systems. Figure reproduced with permission from Wang et al. [8].

Table 1
Clinical and pharmacokinetic considerations for tranexamic acid [7,15,16,158].

Brand name, formulations	Cost (generic)	Half-life	FDA indications	Off-label uses	Adverse events	Routes of administration
Cyklokapron® 1000 mg/10 mL solution for injection 1000 mg/100 mL NaCl solution for injection Lysteda® 650 mg oral tablet	$5.30–86.80 per vial $25 per bag $5.22 per tablet	2 h 11 h	Short-term hemorrhage prevention or reduction in hemophilia patients undergoing tooth extraction Control of heavy menstrual cycle bleeding	• Trauma • Postpartum hemorrhage • Traumatic brain injury • Intracranial hemorrhage • Epistaxis • Oropharyngeal bleeding • Localized bleeding • ACE-inhibitor induced angioedema • Gastrointestinal bleeding • Hemoptysis • Thrombolytic associated hemorrhage • Various surgical indications	• Nausea • Vomiting • Diarrhea • Allergic dermatitis • Hypotension • Hypersensitivity reactions • Dizziness • Visual disturbances • Thromboembolic events • Seizures	Common • Intravenous • Oral • Nebulization • Topical Investigational or military use • Intramuscular • Intraosseous

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Tranexamic acid is commercially available in oral and intravenous (IV) formulations (Table 1) [15,16]. The IV route is preferred in systemic bleeding conditions, such as trauma or postpartum hemorrhage (PPH); for localized bleeding, TXA is commonly administered via nebulization or applied topically due to minimal systemic absorption [17,18]. Intramuscular (IM) TXA has demonstrated similar bioavailability to IV and reaches therapeutic concentrations within 15 min [19-22]. Rapid IV administration (>100 mg/min) may cause hypotension per the manufacturer; however, this claim is debated as it is not widely substantiated in the literature [7,23]. Intraosseous (IO) and IV push TXA are commonly used in military settings and are recommended by the 2020 Tactical Combat Casualty Care Guidelines for Medical Personnel [24-28]. These routes of administration may provide an alternative in patients without vascular access and in settings where access to advanced medical care is limited. Additional research is needed to illustrate the safety of IM, IO, or rapid IV push TXA in civilian settings before it can be routinely recommended in clinical practice.

3. Emergency department applications of tranexamic acid

3.1. Postpartum hemorrhage

Postpartum hemorrhage is an obstetric emergency which accounts for 27.1% of maternal deaths worldwide and 16.3% in developed countries [29]. In addition to fluid and blood product resuscitation and uterotonic agents, the WHO recommends early use of TXA as part of the standard treatment package for all PPH cases, while the American College of Obstetricians and Gynecologists recommends TXA when initial medical management fails [4,30].

Evidence for TXA in the management of PPH is largely driven by the results of the World Maternal Antifibrinolytic (WOMAN) trial, an international randomized controlled trial (RCT) in women with PPH across 193 hospitals [31]. This study was performed with the hypothesis that TXA may be beneficial in PPH, similar to its observed effect of reducing blood loss in surgical populations. Patients were randomized to receive placebo or TXA 1 g IV over 10 min, with an optional repeat dose if bleeding persisted after 30 min or within the first 24 h. Results revealed no difference in the composite primary endpoint of all-cause mortality or hysterectomy (Table 2). Individual components of the composite endpoint were also similar between groups. Death from PPH was 1.5% in the TXA group vs. 1.9% in the placebo group (RR 0.81, 95% CI 0.65–1.00; $p = 0.045$). Death due to other causes was not statistically different between groups. Adverse event rates were also similar. A subgroup analysis of women treated with TXA within 3 h of giving birth demonstrated a significant reduction in death from bleeding. Major criticisms of this trial focus on the study's outcomes and patient population. The confidence interval for death from PPH includes 1 and is therefore not statistically significant. This suggests that TXA's effect on this outcome was modest and warrants further investigation. Controversy on the utility of disease-specific mortality as a surrogate outcome of all-cause mortality also exists, as critics argue this outcome is subjective and not patient-oriented. It is also unclear how TXA improves death from PPH, while having no effect on overall mortality; this would suggest a potential negative impact on other causes of death. Lastly, conduction of the trial in countries with limited resources, such as Nigeria and Pakistan, limits the generalizability to developed countries with lower baseline mortality in women with PPH and greater access to advanced medical care. (See Table 3.)

An open-label RCT in 144 women in France with PPH >800 mL who received high-dose TXA (4 g IV over 1 h, followed by 1 g/h for 6 h) or usual care found significantly decreased blood loss in the TXA group [32]. A meta-analysis of the WOMAN trial and the aforementioned French study found a significantly decreased rate of hysterectomy in TXA treated patients. All-cause mortality and death due to bleeding were not different between groups [33]. A Cochrane Review, which also included both trials, was unable to find a significant difference in rate of hysterectomy, all-cause mortality, or bleeding-related death [34].

Clinical application: The magnitude of benefit of TXA in the management of PPH in developed countries is unclear and further research is needed; however, administration of TXA, in addition to conventional therapies, is reasonable, as it may have a positive effect on mortality and adverse effects appear to be limited (Table 3).

3.2. Trauma

Hemorrhagic shock is responsible for 30 to 40% of deaths in trauma patients and is especially significant early after injury [35]. Damage control resuscitation is recommended in trauma patients at risk of death from hemorrhage to control blood loss until definitive hemostasis is attained [3]. Components of this multi-modal treatment strategy include massive transfusion with blood products and hemostatic therapies, such as TXA [3].

Tranexamic acid was previously found to reduce blood loss in surgical procedures, and due to similarities in hemostatic responses after surgery and trauma, TXA was hypothesized to be beneficial in trauma patients [36]. This prompted the conduction of the landmark Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage-2 (CRASH-2) trial, which serves as the foundation for TXA use in trauma resuscitation today [36]. CRASH-2 was an international RCT which compared TXA to placebo in over 20,000 patients with, or at risk of, significant hemorrhage from trauma. Tranexamic acid was administered as 1 g IV over 10 min, followed by 1 g IV over 8 h, and this dosing strategy has been widely adopted as a standard TXA regimen. Patients treated with TXA had reduced all-cause mortality at 28 days and death due to bleeding (Table 2). Blood product usage and vascular occlusive events were similar between groups. An exploratory analysis of the CRASH-2 trial found that TXA was associated with a decreased risk of death due to bleeding when administered in less than 3 h from time of injury; conversely, an increased risk of death due to bleeding was observed after 3 h [37]. Through a meta-analysis of the CRASH-2 and WOMAN trials, it was estimated that every 15-minute delay in treatment with TXA leads to a 10% decrease in survival from bleeding, and no benefit is observed after 3 h [38].

Some results of the CRASH-2 trial are noteworthy. Patients in both groups had a similar incidence of need for surgery and blood product transfusion, as well as mean amount of blood products administered. These balanced outcomes of surrogate markers for severity of hemorrhage indicate that the mechanism behind TXA's reduction in death due to bleeding is incompletely understood. Furthermore, the investigators did not describe a protocolized method of identifying vascular occlusive events, suggesting these events may have been underreported.

External validity of the CRASH-2 trial is limited due to the study settings and patient population. Selection bias may have played a role in patient selection, as physicians were able to exclude patients in which they judged TXA to be clearly indicated. As CRASH-2 was the first study to evaluate TXA in trauma patients, it is unclear how this assessment was determined. Additionally, most patients enrolled had a systolic blood pressure (SBP) ≥90 mmHg, Glasgow Coma Scale (GCS) score between 13 and 15, and only about half required blood transfusion, suggesting injuries were less critical than anticipated. Lastly, patients in CRASH-2 were predominantly treated in countries with limited availability of blood products, emergency surgeries, and advanced trauma care, which may not be generalizable to contemporary trauma centers in developed countries [39].

Results from smaller, nonrandomized studies in sophisticated trauma centers are inconclusive, but many suggest a lack of benefit of TXA in these settings. A retrospective study evaluating 300 critically ill patients at a Level I Trauma Center who required emergency surgery or transfusions found a higher mortality rate in TXA treated patients [40]. This finding was consistent across all subgroups analyzing time to TXA. A prospective study of 385 severely-injured trauma patients in

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Table 2
Select randomized controlled trials.

Author, year	Groups, time window	Results (TXA vs. comparator)	Conclusion
Postpartum hemorrhage			
WOMAN Trial Collaborators, 2017 [31]	• TXA, $n = 10{,}051$ • Placebo, $n = 10{,}009$	• *All-cause mortality or hysterectomy:* 5.3% vs. 5.5% [$p = 0.65$] • *Death due to bleeding:* 1.5% vs. 1.9% [$p = 0.045$] ○ *Within 3 h:* 1.2% vs. 1.7% [$p = 0.008$] ○ *Greater than 3 h:* 2.6% vs. 2.5% [$p = 0.7$] • *Adverse events:* similar between groups	• TXA did not improve mortality • TXA reduced death due to bleeding, but clinical importance of this outcome is unclear
Trauma			
CRASH-2 Trial Collaborators, 2010 [36]	• TXA, n = 10,096 • Placebo, n = 10,115 • Within 3 h of injury	• *All-cause mortality*: 14.5% vs. 16% [$p = 0.0035$] • *Death due to bleeding*: 4.9% vs. 5.7% [$p = 0.0077$] • *Myocardial infarction*: 0.3% vs. 0.5% [$p = 0.035$] • *Other adverse events:* similar between groups	• TXA improved overall mortality
Guyette et al., 2020 [48]	• TXA, $n = 447$ • Placebo, $n = 456$ • Within 2 h of injury	• *Mortality at 30 d:* 8.1% vs. 9.9% [$p = 0.17$] • *Adverse events:* similar between groups	• TXA did not improve mortality
Traumatic brain injury			
CRASH-3 Trial Collaborators, 2019 [53]	• TXA, $n = 4613$ • Placebo, $n = 4514$ • Within 3 h of injury	• *Head injury-related death (28 d):* 18.5% vs. 19.8%, RR 0.94 [95% CI 0.86–1.02] ○ *Mild-moderate TBI:* RR 0.78 [95% CI 0.64–0.95] ○ *Moderate-severe TBI:* RR 0.99 [95% CI 0.91–1.07] • *All-cause mortality:* RR 0.96 [95% CI 0.89–1.04] • *Adverse events:* similar between groups	• TXA did not improve mortality or head injury-related death • TXA reduced TBI-related death in a subgroup analysis of mild-moderate TBI, but clinical importance of this outcome is unclear
Rowell et al, 2020 [66]	• TXA IVB, $n = 345$ • TXA IVB/CIV, $n = 312$ • Placebo, $n = 309$ • Within 2 h of injury	Results reported as TXA composite vs. placebo • *Good neurologic function (6 mo):* 65% vs. 62% [$p = 0.16$] • *Mortality (28 d):* 14% vs. 17% [$p = 0.26$]	• TXA did not improve neurologic function or mortality
Intracerebral hemorrhage			
Sprigg et al., 2018 [72]	• TXA, $n = 1161$ • Placebo, $n = 1164$ • Within 8 h of symptom onset	• *Functional status (90 d):* aOR 0.88 [95% CI 0.76–1.03] • *Mortality (7 d):* 9% vs. 11% [$p = 0.0406$] • *Mortality (90 d):* 22% vs. 21% [$p = 0.37$]	• TXA did not improve functional outcomes • TXA decreased mortality at 7 days, but was similar by 90 days
Subarachnoid hemorrhage			
Post et al., 2021 [86]	• TXA, $n = 480$ • Usual care, $n = 475$ • Started upon CT diagnosis	• *Good clinical outcome (6 mo):* 60% vs. 64%, aOR 0.86 [95% CI 0.66–1.12] • *Mortality (30 d):* 22% vs. 22%, aOR 0.98 [95% CI 0.72–1.33] • *Mortality (6 mo):* 27% vs. 24%, aOR 1.15 [95% CI 0.86–1.55] • *Adverse events:* similar between groups	• TXA did not improve clinical outcomes or mortality
Gastrointestinal bleeding			
HALT-IT Trial Collaborators, 2020 [94]	• TXA, $n = 5994$ • Placebo, $n = 6015$	• *Death due to bleeding (5 d):* 4% vs. 4%, RR 0.99 [95% CI 0.82–1.18] • *Mortality (30 d):* 9.5% vs. 9.2%, RR 1.03 [0.92–1.16] • *VTE:* 0.8% vs. 0.4%, RR 1.85 [95% CI 1.15–2.98] • *Seizure:* 0.6% vs. 0.4%, RR 1.85 [95% CI 1.03–2.93]	• TXA did not improve mortality or death due to bleeding • TXA caused more VTE and seizures
Epistaxis			
Zahed et al., 2013 [101]	• TXA, $n = 107$ • ANP, $n = 109$	• *Bleeding cessation (10 min):* 71% vs. 31.2% [$p < 0.001$] • *Discharged (2 h): 95.3%* vs. *6.4%* [$p < 0.001$] • *Rebleeding (24 h):* 4.7% vs. 11% [$p = 0.128$]	• TXA improved early bleeding cessation discharge within 2 h
Zahed et al., 2018 [105]	• TXA, $n = 62$ • ANP, $n = 62$	• *Bleeding cessation (10* min*):* 73% vs. 29% [$p < 0.001$] • *Discharged (2 h):* 97% vs. 13% [$p < 0.001$] • *Rebleeding (7 d):* 5% vs. 21% [$p = 0.007$]	• TXA improved early bleeding cessation and discharge within 2 h
Morgenstern et al, 2018 [106]	• TXA, n = 62 • ANP, n = 62	• *Hemostasis (10* min*):* 73% vs. 29% [$p < 0.001$] • *Discharged (2 h):* 97% vs. 21% [$p < 0.001$] • *Rebleeding (7 d):* 5% vs. 21% [$p = 0.007$]	• TXA improved early hemostasis and discharge within 2 h
Akkan et al., 2019 [102]	• TXA, $n = 45$ • ANP, n = 45 • Placebo, n = 45	Results reported as TXA vs. ANP vs. placebo • *Bleeding cessation (15* min*):* 93.3% vs. 91.1% vs. 71.1% • *No rebleeding (24 h):* 86.7% vs. 73.3% vs. 60%	• TXA did not improve early bleeding cessation vs. ANP • TXA caused less rebleeding at 24 h
Amini et al., 2021 [107]	• TXA, $n = 50$ • PANP, n = 50	• *Time to bleeding cessation*: 6.7 vs. 11.5 min [$p = 0.002$] • *Rebleeding (72 h):* 6% vs. 20% [$p = 0.03$]	• TXA decreased time to bleeding cessation and rebleeding at 72 h
Reuben et al., 2021 [108]	• TXA, $n = 254$ • Placebo, $n = 242$	• *Need for ANP:* 43.7% vs. 41.3% [$p = 0.59$] • *Hospital admission:* 43.3% vs. 45.5%, OR 0.92 [0.64–1.32] • *Rebleeding:* 19.4% vs. 16.1%, OR 1.26 [0.79–2]	• TXA did not improve need for ANP, hospital admission rate, or rate of rebleeding

ANP: anterior nasal packing, aOR: adjusted odds ratio, CIV: continuous infusion, IVB: intravenous bolus, PANP: phenylephrine and lidocaine-soaked anterior nasal packing, RR: risk ratio, TBI: traumatic brain injury, TXA: tranexamic acid, VTE: venous thromboembolism.

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the United Kingdom (UK) also demonstrated no mortality benefit for TXA compared to non-TXA treated patients [41]. Patients in the TXA group appeared more critically ill, as they required more blood products and sooner emergency surgery. In a multivariate analysis in patients with shock, TXA was independently associated with a reduction in multi-organ failure and all-cause mortality. A prospective cohort study of 422 trauma patients in the Netherlands found TXA treated patients to have similar outcomes as non-TXA treated patients; although, patients in the TXA group appeared to be more severely-injured and may have confounded the results [42].

In a military setting, the Military Application of Tranexamic Acid in Trauma Emergency Resuscitation (MATTERs) Study retrospectively compared TXA administration to no TXA in patients receiving at least 1 unit of packed red blood cells after combat-related injury [27]. TXA was associated with lower mortality within 48 h as well as in-hospital mortality. This benefit was greatest in patients who required massive transfusion. Higher rates of thrombotic events occurred in TXA treated patients. Conversely, a larger retrospective study in combat trauma patients was unable to demonstrate a statistically significant association between TXA use and mortality; however, authors report the study was underpowered [43]. An increased risk of venous thromboembolism (VTE) was also observed.

A meta-analysis evaluating the impact of TXA in both military and civilian setting found similar overall mortality between TXA and non-TXA treated patients [44]. Analyses of patients in civilian settings demonstrated a lower mortality rate with TXA, while mortality was higher when TXA was administered in military settings. In a subgroup analysis by study design type, TXA was only associated with lower mortality in RCTs.

To expand on the findings that earlier TXA may be most beneficial, a number of nonrandomized studies were performed in the prehospital setting. In a multicentered, prospective, observational study in 362 trauma patients with signs of hemorrhagic shock, TXA treated patients had lower 28-day mortality and blood product use [45]. The mortality benefit was greatest in more severely injured patients. A retrospective study of 4550 severely-injured trauma patients in Germany found that prehospital TXA was associated with lower mortality within 6 and 12 h compared to a propensity score matched cohort who did not receive prehospital TXA; however, groups had similar mortality rates at 24 h and 30 days [46]. Another retrospective study of 1333 trauma patients in the United States (US) found similar rate of VTE between TXA and non-TXA treated patients; in-hospital mortality was lower in the TXA group [47].

The most robust data for prehospital TXA comes from the Study of Tranexamic Acid During Air and Ground Medical Prehospital Transport (STAAMP) trial, which compared prehospital TXA 1 g IV over 10 min to placebo in 903 trauma patients at risk of hemorrhage [48]. Patients were transported to one of four Level I Trauma Centers in the US after enrollment. Mortality at 30 days and adverse events were similar between groups (Table 2). The trial was stopped early due to slow enrollment and did not reach power to detect a difference in the primary outcome. In pre-specified post hoc analyses, TXA was associated with reduced mortality when administered within 1 h of injury, in patients with severe shock, and in those who received a repeat bolus dose regimen totaling 3 g of TXA. Findings from a secondary analysis of the STAAMP trial demonstrated lower 30-day mortality, transfusion requirements, and incidence of multiorgan failure in patients with a shock index ≥0.9 who were treated with TXA within 1 h of injury [49].

The ongoing Pre-hospital Anti-fibrinolytics for Traumatic Coagulopathy and Haemorrhage (PATCH-Trauma) trial aims to address gaps in the current literature. Findings from this study should provide insight into TXA's effect on patient-oriented outcomes in trauma patients administered prehospital TXA prior to transport to advanced trauma hospitals [50].

Clinical application: Tranexamic acid may be safe and beneficial in trauma patients at risk of hemorrhage, although the extent of this benefit in advanced trauma centers is unclear. Treatment within 3 h of injury is recommended and may be provided in the prehospital setting; TXA given beyond 3 h may be harmful and should be avoided (Table 3).

3.3. Traumatic brain injury

Traumatic brain injury (TBI) is a leading cause of disability in the US, and contributes to 30% of trauma-related deaths [51]. Intracranial pressure (ICP) management is a principal focus in TBI patients as elevated ICP is known to be associated with increased mortality and poor outcomes [52]. Ongoing bleeding in TBI patients can worsen ICP and TXA has been hypothesized to reduce hemorrhage expansion and brain herniation [53]. Findings from multiple small studies have indeed suggested reduced hemorrhage progression and improved clinical outcomes with TXA, but external validity of these studies is limited [54-60].

The Clinical Randomisation of an Antifibrinolytic in Significant Head Injury-3 (CRASH-3) trial, a landmark placebo-controlled RCT, aimed to further elucidate these findings [53]. This study evaluated TXA (1 g IV over 10 min, followed by 1 g IV over 8 h) in patients with isolated head injury and no major extracranial hemorrhage (Table 2). The study's protocol was amended to include a goal of 10,000 patients within 3 h of injury to evaluate a primary outcome of head injury-related death. Only 9202 patients within the 3-hour time window were eligible for analysis, and findings revealed no difference in head injury-related death between TXA and placebo groups. In subgroup analyses, TXA reduced the risk of head injury-related death in patients with mild to moderate TBI (GCS 9–12), but not in severe TBI (GCS 3–8) or those with an unreactive pupil. A time-to-treatment effect was observed, but only in patients with mild to moderate TBI. Adverse events were similar between groups. Criticisms of this trial include the positive emphasis on findings from a secondary endpoint, which is hypothesis-generating rather than conclusive. Additionally, similar to the WOMAN trial, the utility of disease-specific mortality as a meaningful endpoint is controversial.

Findings from meta-analyses prior to the CRASH-3 trial suggested TXA may improve mortality and hemorrhage expansion in patients with TBI, but does not improve neurologic outcomes or need for neurosurgery [61,62]. A more recent meta-analysis of nine RCTs, including CRASH-3, found no benefit of TXA on mortality or disability, despite a decrease in hematoma expansion [63]. Limitations to these aggregated results include the different enrollment windows and patient GCS scores between trials, as well as the inclusion of patients with extracranial trauma.

Further studies aimed to investigate TXA's effect in patients with TBI of varying severity. Findings from a nested study of the CRASH-3 trial suggest TXA may prevent new intracranial hemorrhage in patients with reactive pupils at baseline. This study was limited by a large proportion of patients without repeat imaging data [64]. The Clinical Randomisation of an Anti-fibrinolytic in Symptomatic Mild Head Injury in Older Adults (CRASH-4) trial is underway to evaluate early IM TXA in patients with mild TBI (NCT04521881) [65]. In an RCT evaluating 966 patients with moderate-severe TBI (GCS ≤12 and SBP ≥90 mmHg), patients were randomized to receive one of two TXA dosing regimens, or placebo within 2 h of injury. Good functional outcome at 6 months, all-cause mortality, and adverse events were similar between groups (Table 2) [66]. In a retrospective study of 1827 patients with suspected severe TBI (GCS ≤8) who were transported to nine trauma centers in the Netherlands, patients who received TXA had comparable rates of mortality to non-TXA treated patients. These findings were consistent in patients with imaging-confirmed TBI; however, a higher mortality rate was found in patients with isolated severe TBI [67].

Clinical application: Insufficient evidence exists to routinely recommend TXA for isolated TBI, but TXA may be considered in patients with TBI and concomitant extracranial traumatic hemorrhage. The effect of TXA on patient-centered outcomes in mild to moderate TBI should be investigated further (Table 3).

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3.4. Spontaneous intracranial hemorrhage

Spontaneous intracranial hemorrhage, also known as hemorrhagic stroke, is responsible for up to 25% of strokes worldwide [68]. This stroke subtype comprises intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH), both of which are associated with significant morbidity and mortality [68,69]. Treatment focuses on halting hemorrhagic progression through blood pressure control, correction of coagulopathy, intracranial pressure management, and surgical intervention [70,71]. These therapies are best employed at centers with advanced stroke and neurosurgical services, which may not be universally accessible. Hemostatic therapies, such as TXA, have been proposed as adjunctive agents to combat coagulopathy and impede hemorrhage expansion in this patient population.

The Tranexamic acid for Hyperacute Primary Intracerebral Haemmorrhage (TICH-2) trial was a landmark international RCT that compared TXA (1 g IV over 10 min, followed by 1 g IV over 8 h) to placebo in 2325 patients with intracerebral hemorrhage (ICH) [72]. Tranexamic acid treated patients had similar functional status at 90 days compared to those who received placebo (Table 2). Despite reduced volume and incidence of hematoma expansion, as well as fewer deaths by day 7 in TXA treated patients, 90-day mortality was similar between groups. A subgroup analysis revealed baseline hematoma volume between 30 mL and 60 mL was associated with improved functional outcome in the TXA group. Authors note that most patients were enrolled after 3 h of symptom onset, which may have affected outcomes in the TXA group, as a time-to-treatment effect has been observed in other bleeding conditions. Future trials should investigate the effect of TXA in ICH within 3 h of symptom onset, and in patients without non-survivable bleeds.

Multiple post-hoc subgroup analyses of the TICH-2 trial have been published. In one analysis, TXA was associated with reduced risk of neurological deterioration within 48 h [73]. Another exploratory analysis found that TXA reduced the risk of ICH expansion in patients overall and in a subgroup of patients on antiplatelet agents. No significant interaction between pre-ICH antiplatelet therapy and TXA was found [74]. In an analysis evaluating the impact of computed tomography spot sign findings, a proposed biomarker of ongoing hematoma expansion, treatment with TXA resulted in similar outcomes compared to placebo among patients with and without spot sign [75].

Studies following the TICH-2 trial found inconsistent results. Smaller multicenter RCTs were unable to demonstrate a benefit of TXA on hematoma expansion or mortality [76,77]. Conversely, a meta-analysis found that TXA was associated with reduced ICH expansion with no increase in thromboembolic events; however, mortality and improved functional outcome at 90 days were similar between groups [78].

Tranexamic acid use in aneurysmal subarachnoid hemorrhage (SAH) has been researched in numerous small studies as early as the 1970s, most of which evaluated courses of TXA given throughout the hospital stay [79]. An RCT in 2002 examined shorter courses of TXA (less than 72 h) and found that TXA reduced rebleeding and mortality [80]. Conversely, Cochrane Reviews have suggested that antifibrinolytics are associated with an increase in cerebral ischemia, despite improvement in rebleeding [81,82]. A retrospective study evaluating patients with aneurysmal SAH found that TXA was not associated with improved rates of rebleeding or functional outcomes at 90 days, though in-hospital mortality was lower in TXA treated patients [83]. In a meta-analysis of 15 studies in 4883 patients which evaluated TXA in SAH and ICH, TXA was associated with reduced mortality [79]. Studies included in this analysis ranged from 1971 to 2021 and findings may not be applicable to current standards of care. Additional limitations include the pooled analysis of SAH and ICH, which have different pathologies and patient populations, inclusion of randomized and non-randomized studies, and risk of publication bias. Other meta-analyses have found no benefit on mortality or good neurologic outcome, despite reductions in rebleeding rates [84,85].

The Ultra-Early Tranexamic Acid After Subarachnoid Haemorrhage (ULTRA) trial is the largest trial investigating TXA's effect on clinical outcomes in aneurysmal SAH to date. This unblinded RCT evaluated 955 patients with SAH presumably due to a ruptured aneurysm and compared placebo to TXA 1 g IV over 10 min, followed by 1 g IV over 8 h [86]. Tranexamic acid did not improve rate of good functional outcome at 6 months, rebleeding, or all-cause mortality (Table 2). Authors note that the inclusion of patients without confirmed aneurysm may have diluted the results. Even so, the median time from symptom onset to TXA administration was 3 h, which may have been beyond the time frame during which most patients experience rebleeding, and thus would be unable to provide a benefit [86,87].

Clinical application: While small studies and meta-analyses suggest TXA may reduce hematoma expansion in ICH, the most rigorous RCT found no benefit in functional status or mortality. Similarly, a large RCT in SAH found no benefit of TXA. Tranexamic acid is not recommended in either patient population (Table 3).

3.5. Gastrointestinal bleeding

Acute gastrointestinal bleeding (GIB) is a common presentation in the ED and carries up to 10% mortality risk [88]. Re-bleeding can occur after initial hemostasis is achieved and may lead to poorer prognosis [88]. Blood product resuscitation and early endoscopy is recommended in the management of GIB; prokinetic and antisecretory therapy may also be considered [89]. However, access to advanced medical care and endoscopic intervention may not be readily accessible in all ED settings, spurring interest in adjunctive treatments.

Early investigation into TXA as a hemostatic agent in patients with GIB began in the 1970s and a pooled analysis of these trials suggested a mortality benefit; however, conclusions from these studies have been difficult to draw due to varying dosing regimens and administration routes, as well as advancement of care in more recent years [90]. Additionally, findings inconsistently demonstrated a benefit in rates of rebleeding, need for endoscopic or surgical intervention, and mortality. Meta-analyses of small studies also previously suggested a benefit of TXA in GIB [91-93]. Due to potential selection and publication biases, these results were considered hypothesis-generating and TXA's role in GIB remained unclear.

In 2020, the landmark trial, Effects of a High-Dose 24-h Infusion of Tranexamic Acid on Death and Thromboembolic Events in Patients with Acute Gastrointestinal Bleeding (HALT-IT), evaluated the utility of TXA in GIB in over 12,000 patients in 15 countries [94]. In this RCT, patients received TXA 1 g IV, followed by 3 g IV infusion administered over 24 h, or placebo. Death due to bleeding was similar between groups; rates of VTE and seizures were significantly higher in patients treated with TXA (Table 2). This was the largest trial published to date in this patient population and has been widely acknowledged as the “nail in the coffin” for TXA in GIB. The high dose of TXA used compared to other trials may have contributed to increased rate of adverse events. Additionally, due to the large proportion of patients with liver disease and low incidence of lower GIB and baseline anticoagulant use, TXA's effect in specific patient populations with varying GI bleed etiologies warrants further investigation.

Few studies have specifically evaluated TXA in lower GIB and results are inconclusive. An RCT of 100 patients with lower GIB found no benefit of oral TXA [95]. A retrospective study of 30,526 Japanese patients with diverticular bleeding found that IV TXA was not associated with improved mortality but may improve other clinical outcomes [96].

Additional studies following the HALT-IT trial continue to yield inconsistent findings. In a single-center retrospective study, patients with GIB and endoscopic verified ulcer found no benefit of TXA on 30-day mortality, rate of rebleeding, or length of stay (LOS). Patients in the TXA group more frequently exhibited overt symptoms of GIB and required more blood products compared to non-TXA treated patients, suggesting the TXA group may have been more critically ill at

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baseline [97]. A meta-analysis of eight studies including nearly 13,000 patients with upper GIB concluded that TXA was associated with reduced rate of rebleeding and need for surgery, without an increase in adverse events; no significant association with mortality or blood transfusion requirements was found [98].

Clinical application: Tranexamic acid is unlikely beneficial and may be harmful in patients with GIB (Table 3).

3.6. Epistaxis

Approximately one in every 200 ED visits in the US is due to epistaxis. While most cases are self-limiting and resolve with conservative measures, up to 6% of patients seek additional medical attention for epistaxis [99]. Conventional treatment options for epistaxis include direct pressure, topical vasoconstrictors and hemostatic therapies, cautery, and anterior nasal packing [99]. While nasal packing is commonly used, it is often painful and requires additional patient follow up [100].

Topical TXA is a noninvasive, low-cost treatment option with minimal systemic absorption or painful side effects [100]. Interest in topically applied TXA for epistaxis rose following publication of a single-center RCT which compared TXA (500 mg soaked in cotton and applied to the bleeding nostril) to anterior nasal packing in 216 patients with anterior epistaxis. Patients treated with TXA demonstrated improved cessation of bleeding within 10 min, a higher rate of discharge within 2 h, and less rebleeding in 24 h (Table 2) [101]. Despite several design limitations, including small sample size, lack of blinding, and exclusion of posterior epistaxis, the signal of benefit encouraged widespread adoption of TXA in the management of epistaxis.

Additional studies continued to support the efficacy of TXA in epistaxis compared to standard therapies, such as local vasoconstrictors and nasal packing, as well as oxymetazoline (Table 2) [102-104]. Similar RCTs in epistaxis patients on antiplatelet agents have also demonstrated beneficial results (Table 2) [105-107]. Due to consistent positive findings, TXA continued to gain extensive popularity in treating epistaxis in the ED.

In 2021, the largest RCT evaluating TXA in this patient population, The Use of Tranexamic Acid to Reduce the Need for Nasal Packing in Epistaxis (NoPAC) trial, was published and the results have led to less certainty about TXA's utility in epistaxis [108]. This multicenter study evaluated 496 patients in the UK with persistent epistaxis despite topical vasoconstrictors. The incidence of nasal packing requirement and secondary outcome measures were similar between TXA and placebo groups (Table 2). Noteworthy points of discussion for this trial include the lack of delineation of epistaxis subtype, later timing of TXA administration in relation to other therapies, lower dose of TXA used (200 mg) compared to previous studies, use of phenylephrine as the topical vasoconstrictor choice, and a nonpatient-centered primary outcome measure. Adverse events were uncommon and included feeling faint, sensation in the nostril, headache, nausea and vomiting, and the difference between groups was not statistically significant.

A recent meta-analysis evaluating 1299 patients in eight studies, including the NoPAC trial, found that TXA treated patients were 3.5 times more likely to achieve early hemostasis and less likely to experience rebleeding at 24–72 h [109]. Authors concluded that TXA was associated with improved rates of bleeding cessation compared to standard therapies.

Clinical application: While the magnitude of TXA's benefit in epistaxis may be smaller than previously perceived, the risk of adverse events appears low. As such, TXA is reasonable to consider in the management of epistaxis, in addition to other standard therapies (Table 3).

3.7. Hemoptysis

Hemoptysis is a symptom of diverse conditions causing bleeding from the respiratory tract. It is often described as non-massive and massive or life-threatening, with the latter loosely defined as 200–1000 mL of blood expectorated in 24 h [110]. However, blood volume loss prior to medical evaluation is often difficult to quantify and may be underestimated [110]. Non-massive hemoptysis is commonly managed with medical therapies, such as local vasoconstrictors and hemostatic therapies [110,111]. Conventional management of massive hemoptysis primarily involves invasive intervention with airway control, bronchoscopy, and endoscopy [110].

Administration of TXA via nebulization for the management of hemoptysis is increasingly described in the literature. Many case reports and case series have depicted successful bleeding cessation with nebulized TXA in patients with hemoptysis and concomitant bronchiectasis, pulmonary embolism, pulmonary hemorrhage, and after systemic thrombolysis [112-118]. Doses utilized ranged from 500 to 2000 mg over 10 to 20 min and were administered undiluted or diluted with sodium chloride 0.9%. In 2018, an RCT compared nebulized TXA 500 mg three times daily to placebo in 47 patients with non-massive hemoptysis and found a higher rate of bleeding resolution in TXA treated patients [119].

Intravenous TXA has also been investigated in this patient population. An RCT in 66 patients with non-massive hemoptysis found that IV TXA (1 g IV over 10 min, followed by 1 g IV over 8 h) reduced hemoptysis by day 2 with no adverse events noted [120]. A retrospective review of 9933 matched pairs of patients admitted for non-massive hemoptysis in Japan found that IV TXA was associated with reduced mortality, shorter LOS, and lower healthcare costs compared to no TXA [121]. A meta-analysis of four small RCTs and two retrospective studies of patients with hemoptysis echoed these findings and concluded that TXA use was associated with lower short-term mortality, reduced bleeding time, shorter hospital LOS, and less need for intervention [122]. The small sample sizes of the RCTs included, as well as the heterogeneity of study designs, TXA dosing, and hemoptysis etiology, preclude the ability to draw definitive conclusions.

Clinical application: Limited evidence suggests that nebulized and IV TXA for non-massive hemoptysis may be safe and effective; it is also reasonable to include TXA in the management of massive hemoptysis (Table 3).

3.8. Oropharyngeal and localized bleeding

Tranexamic acid has also been described in the literature for the management of acute oropharyngeal bleeding. An RCT in 37 patients on warfarin presenting with post-tooth extraction hemorrhage compared compression with TXA-soaked gauze to a control group [123]. Time to achieve hemostasis was improved and hemorrhage was better controlled at 24 h in TXA treated patients. A retrospective study in patients who presented to the ED for oral bleeding found that TXA was associated with improved hemostasis [124]. Nebulized TXA has also been reported as a useful adjunct in adults and children post-tonsillectomy hemorrhage (PTH) [125-127]. In a small retrospective study of children presenting with PTH, nebulized TXA was associated with reduced need for surgical intervention without any adverse events reported [128].

Various case reports have also described the application of topical TXA in the management of localized bleeds. The most common dose and formulation reported in these cases was 500 mg IV TXA soaked in gauze and applied to the bleeding site. Types of bleeds depicted included nipple piercing site bleeding in a hemophilia patient, arteriovenous fistula site bleeding, and post-procedural rectal bleeding [129-131]. The use of crushed TXA 500 mg tablets applied topically has also been reported in a case series of two patients with hemophilia and skin ulcers. Both cases resulted in wound healing after a few weeks of therapy [132].

Clinical application: Based on limited available evidence, topical and nebulized TXA may be an option for the management of oropharyngeal bleeding. Topically applied TXA for localized bleeding may also be considered. (Table 3).

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Table 3
Summary of evidence-based recommendations for tranexamic acid utilization in various clinical settings.*

Clinical setting	Level of evidence	TXA dosing regimens described in the literature	Guideline and clinical policy recommendations (USA)
Likely beneficial			
Trauma	RCT	1 g IV over 10 min, followed by 1 g IV over 8 h Give within 3 h of injury Beyond 3 h may be harmful	ACS TQIP (2014) [1] - Antifibrinolytic agents can be used empirically or in response to findings of increased fibrinolytic activity EAST (2017) [3] - In adult patients with severe trauma, we conditionally recommend the use of TXA as an in-hospital hemostatic adjunct in comparison to no TXA
Unclear if beneficial			
Postpartum hemorrhage	RCT	1 g IV over 10 min, followed by 1 g IV over 8 h Give within 3 h of delivery	ACOG (2017) [4] - Tranexamic acid should be considered in the setting of obstetric hemorrhage when initial medical therapy fails
Traumatic brain injury	RCT	1 g IV over 10 min, followed by 1 g IV over 8 h Give within 3 h of injury	No mention of TXA in any related guideline
Epistaxis	RCT	200–500 mg soaked in cotton and applied to bleeding nostril, or administered via nasal atomizer	AAO-HNS (2020) [99] - Additional study of TXA is needed to understand indications and efficacy for nosebleed control
Hemoptysis	RCT (small)	1 g IV over 10 min, followed by 1 g IV over 8 h, or 500–2000 mg via nebulizer over 10–20 min; may dilute with 5 mL sodium chloride 0.9% to mitigate precipitation in nebulizer	No pertinent guideline available
Oropharyngeal or localized bleeding	RCT (small)	250–500 mg soaked in compression gauze and applied to bleeding area for oral/local bleeding 250–1000 mg via nebulizer for post-tonsillectomy bleeding; may dilute with 5 mL sodium chloride 0.9% to mitigate precipitation in nebulizer	No pertinent guideline available
Thrombolysis-induced major bleeding	Case reports	1 g IV over 10 min	NCS/SCCM (2016) [2] - In cases where cryoprecipitate is contraindicated or not available in a timely manner, we suggest using an antifibrinolytic agent [in sICH] AHA/ASA (2017) [5] - There are limited data on the safety and efficacy of antifibrinolytic agents in sICH - These agents, however, may be considered in all patients with sICH, particularly those who decline blood products
ACEI-induced angioedema	Case series	1 g IV over 10 min	AAEM (2021) [142] - There are insufficient data to support the use of tranexamic acid in ACEI induced angioedema
Unlikely beneficial			
Intracerebral hemorrhage	RCT	1 g IV over 10 min, followed by 1 g IV over 8 h	No mention of TXA in any pertinent guideline
Subarachnoid hemorrhage	RCT	1 g IV, followed by 125 mg/h, until aneurysm treatment, or 24 h duration	AHA/ASA (2012)** [71] - For patients with an unavoidable delay in obliteration of aneurysm, a significant risk of rebleeding, and no compelling medical contraindications, short-term (<72 h) therapy with tranexamic acid or aminocaproic acid is reasonable to reduce the risk of early aneurysm rebleeding
Unlikely beneficial, may be harmful			
Gastrointestinal bleeding	RCT	1 g IV, followed by 3 g IV over 24 h	No mention of TXA in any pertinent guideline

AAEM: American Academy of Emergency Medicine, AAO-HSN: American Academy of Otolaryngology-Head and Neck Surgery, ACOG: American College of Obstetricians and Gynecologists, ACS: American College of Surgeons, AHA: American Heart Association, ASA: American Stroke Association, ACEI: Angiotensin converting enzyme inhibitor, EAST: Eastern Association for the Surgery of Trauma, NCS: Neurocritical Care Society, RCT: randomized controlled trial, SCCM: Society of Critical Care Medicine, sICH: symptomatic intracranial hemorrhage, TQIP: Trauma Quality Improvement Program; TXA: tranexamic acid; USA: United States of America.

* Recommendations concluded through author consensus based on available evidence.

** Published prior to trial by Post et al.

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3.9. Thrombolysis-induced major bleeding

Thrombolytic agents activate plasminogen conversion to plasmin to promote lysis of fibrin, leading to clot degradation. Alteplase and tenecteplase are the most common thrombolytics used in ED settings for the management of ischemic conditions, such as myocardial infarction, massive pulmonary embolism, and acute ischemic stroke. Both agents share the same mechanism of action; however, tenecteplase is more fibrin-specific and possesses a longer duration of action. Despite the short plasma half-lives of alteplase and tenecteplase (up to 5 min and 24 min, respectively), hypofibrinogenemia following thrombolysis can persist for hours and lead to prolonged coagulopathy [2,133-135]. Cryoprecipitate is the preferred treatment for thrombolytic-induced ICH and may be considered up to 24 h after exposure [2]. Tranexamic acid's opposing mechanism of action counteracts the effect of alteplase and theoretically may stabilize coagulopathy and prevent hematoma expansion. As such, guidelines recommend TXA as a second-line agent for thrombolysis-induced ICH [2].

Evidence for TXA for thrombolysis reversal is limited to three case reports of patients with alteplase-induced hemorrhage, including pulmonary hemorrhage, pericardial effusion with tamponade, and intraparenchymal hemorrhage [116,136,137]. The use of aminocaproic acid, an antifibrinolytic agent similar to TXA, in the setting of alteplase-induced ICH has also been described in a case series and within retrospective studies [138-140]. No literature is available for the use of TXA to manage tenecteplase-induced major bleeding.

Clinical application: The quality of evidence for TXA in reversal of alteplase-induced hemorrhage is low; however, in cases of life-threatening bleeding following thrombolysis, such as ICH, TXA is reasonable to consider (Table 3). It may also be reasonable to consider TXA in the management of tenecteplase-induced ICH due to its similar mechanism of action to alteplase; however, there is a paucity of data to support this recommendation.

3.10. Angiotensin converting enzyme inhibitor-induced angioedema

Angiotensin converting enzyme (ACE) inhibitor-induced angioedema (ACEI-AE) is mediated through blockade of bradykinin inactivation via inhibition of ACE, the primary enzyme involved in bradykinin degradation (Fig. 1) [141]. There are currently no standard of care diagnostic tools or treatment options for ACEI-AE and airway stabilization remains primary focus of management [142]. The American Academy of Emergency Medicine does not endorse routine use of any specific medication therapy for ACEI-AE due to lack of high-quality supporting evidence [142].

Patients presenting to the ED with angioedema are commonly treated with histamine-targeted medications and steroids for empirical treatment of allergic reaction and anaphylaxis; however, these are unlikely beneficial in ACEI-AE [143]. Evidence for bradykinin-targeted therapies used in hereditary angioedema, such as icatibant or C1 esterase inhibitor, is inconclusive and their utilization for ACEI-AE is controversial. In addition, the high cost and lack of widespread availability of these agents prohibit routine use. Fresh frozen plasma has been evaluated in small retrospective studies for ACEI-AE, as it contains enzymes needed to break down bradykinin; however, it also contains substrates for bradykinin formation and the impact of these opposing mechanisms requires additional investigation [142].

Tranexamic acid is a second-line agent in prophylactic management of hereditary angioedema and has also been proposed as an inexpensive treatment option in ACEI-AE due to its role in the kallikrein–kinin pathway to impede bradykinin production (Fig. 1) [8,142]. A retrospective review of 33 ED patients with severe ACEI-AE found 81.8% of patients achieved significant improvement after treatment with TXA and no deaths, adverse events, or progression requiring intubation occurred [144]. Most patients in this study received TXA 1 g IV. Extensive interpretation of this article was limited due to publication in French. In the US, several case reports have described the use of TXA in the management of ACEI-AE [8,145,146]. A recently published retrospective review of patients with ACEI-AE found 14 of 16 patients who received TXA did not require intubation; the remaining two patients were intubated prior to TXA administration. All but one of these patients received TXA 1 g IV over 10 min and none experienced adverse effects [147].

Clinical application: While the evidence for TXA in ACEI-AE is limited to small retrospective studies, a single dose of IV TXA may be reasonable, as it targets the theoretical pathogenesis of ACEI-AE, is inexpensive, widely available, and adverse effects may be outweighed by potential avoidance of intubation (Table 3).

3.11. Viscoelastography-guided tranexamic acid

The utility of viscoelastography, such as thromboelastography (TEG) or rotational thromboelastometry (ROTEM), to assess coagulopathy and fibrinolysis during active hemorrhage is increasingly described in the literature [148-151]. These point-of-care tests may aid in identifying patients which may benefit most from TXA and guide hemorrhage management. In trauma patients, a spectrum of fibrinolysis occurs, including hyperfibrinolysis, physiologic fibrinolysis, and hypofibrinolysis (fibrinolytic shutdown) [152]. Patients transition between these phenotypes as time from injury elapses [152]. Administration of an antifibrinolytic, such as TXA, to patients with physiologic fibrinolysis or hypofibrinolysis may be harmful, and a phenotype-targeted approach using TEG may be preferred [153,154]. In an analysis of patients with severe trauma who developed hyperfibrinolysis, TXA was associated with improved survival at 6 h; survival beyond 6 h was similar to non-TXA treated patients [155]. Another analysis of an RCT in traumatic brain injury (TBI) patients found no differences in fibrinolysis based on TEG results between TXA and placebo groups [156]. A recent analysis in trauma patients who underwent ROTEM testing found that TXA was associated with reduced early mortality and did not increase late mortality, regardless of fibrinolysis transition pattern [157]. Large RCTs evaluating the effect of TXA in TEG-driven protocols for the management of active hemorrhage of varying etiologies and fibrinolytic phenotypes are needed.

4. Conclusion

Definitive management for ongoing hemorrhage is source control, and airway management remains the cornerstone of care for ACEI-AE; however, supportive therapies, such as TXA, can play an important role. Tranexamic acid has been incorporated into treatment algorithms for a multitude of conditions encountered in the ED and the evidence surrounding TXA continues to evolve. The most robust trials suggest TXA may offer a modest mortality benefit in trauma patients at risk of significant bleeding, but is not beneficial in spontaneous intracranial hemorrhage or gastrointestinal bleeding. The utility of TXA in other clinical scenarios is less clear and requires clinical judgment. Serious adverse events related to TXA, including thromboembolic complications and seizures, are uncommon and may be correlated with higher systemic doses than commonly used in clinical practice. While additional research is needed to identify patients most likely to benefit from TXA, TXA appears to be a reasonable adjunct for the emergency medicine clinician to consider.

Declarations of Competing Interest

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Credit authorship contribution statement

Kellie Wang: Writing – review & editing, Writing – original draft. **Ruben Santiago:** Writing – review & editing, Writing – original draft, Conceptualization.

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